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(54) Title: FORMULATION FOR DELIVERY OF PARTICULATE MATERIAL TO MUCOSAL MEMBRANES

(57) Abstract

A delivery formulation for administration to a mucous membrane and which is either mucoadhesive per se or becomes mucoadhesive on contact with a mucous membrane, said formulation comprising a particulate material to be delivered to or across the membrane in a matrix or dose form containing an amphiphilic substance. Prefered formulations in accordance with the invention comprise a matrix or dose form of the amphiphilic substance in a liquid crystal phase, the matrix or dose form incorporating the particulate material to be delivered.

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FORMULATION FOR DELIVERY OF PARTICULATE MATERIAL TO MUCOSAL MEMBRANES

The present invention relates to a formulation and method for the delivery of agents, e.g. diagnostic or therapeutic agents, across a mucosal membrane.

Various formulations are known for the delivery of therapeutic agents across "surfaces" of the body. A number of such formulations are based on the use of amphiphilic substances, i.e. compounds having both "hydrophilic" and "hydrophobic" character. Examples of such amphiphilic molecules include mono, di-, or tri-acyl esters of glycerol with a long chain (e.g. C_{12}-C_{20}) carboxylic acid (usually but not necessarily one having a degree of unsaturation). A particular example of an amphiphilic substance is glycerol monooleate (monoolein).

Thus, for example, GB-A-2 212 723 proposes a transdermal delivery formulation comprised of a matrix of glycerol monooleate incorporating, as a therapeutic agent to be delivered, a steroid, a nitrate or bisperiden. The formulation is stated to be particularly useful for the delivery of the therapeutic agents across skin although it is also a stated object of the invention of GB-A-2 212 723 to increase the permeability of body surfaces including the mucous and other membranes.

The use of amphiphilic diacyl glycerides has also been proposed in pharmaceutical formulation. Thus, for example, WO-A-9534287 discloses a biologically active composition comprised of (a) a diacyl glycerol, (b) a phospholipid and, optionally, (c) a polar liquid in such proportions that they together form an L2-phase or a cubic crystalline phase, the composition incorporating a biologically active material dissolved or dispersed therein. The biologically active material may for example be an antibiotic, antimycotic, protein, peptide, steroid, local anaesthetic, chemotherapeutic agent or an antiviral substance. Compositions as disclosed in WO-A-9534287 are proposed for a number of uses, e.g. parenteral administration of drugs, administration of drugs for treating paradontosis, preparation of depot formulations, enhancing absorption of proteins and peptides, and for treating infections in or adjacent mucous membranes.

WO-A-9526715 discloses bioadhesive/mucoadhesive drug delivery formulations which contain a therapeutic agent and which are intended for application to or through undamaged or damaged skin or mucosa of an animal so as to remain in contact with the skin or mucosa for an extended period of time to prolong delivery of the drug. Such formulations have the benefit that the drug delivery system can be localised on a specific site for the purpose of local therapy, e.g. for the purpose of targeting specific diseased tissue.

The formulation of WO-A-9726715 comprises the therapeutic agent in admixture with a fatty acid ester having a molecular weight below about 1000 daltons. The bioadhesive nature of the formulation is achieved by "contact" of the ester with a hydrophilic medium, e.g. water. Thus, the formulation of WO-A-9526715 may be bioadhesive/mucoadhesive in the form in which it is to be administered (by virtue of the formulation having been prepared with water or glycerol) or may become bioadhesive/mucoadhesive only on contact with body fluids associated with the tissue to which the formulation is administered. In many cases, the bioreductive/mucoadhesive formulations of WO-A-9526715 incorporate a liquid crystalline phase formed by the fatty acid ester and the hydrophilic liquid.

A wide range of therapeutic agents is listed in WO-A-9526715, many of which are relatively small molecules. It is however also contemplated in WO-A-9526715 that the therapeutic agent may be a sulfated polysaccharide, e.g. heparin, which is of high molecular weight. Other high molecular weight therapeutic agents which the skilled person would contemplate for incorporation in the delivery formulations of WO-A-9526715 would include such agents having a molecular weight in excess of 5000 or 10000 daltons and would include proteins and nucleic acids although there would be the disadvantage of a significant degradation of such "naked" molecules.

WO-A-9323025 also gives a summary of the liquid crystalline phases formed when amphiphilic molecules are admixed with polar liquids such as water.

Thus the prior art has addressed the delivery of various drugs across skin and mucosal membranes using the permeation enhancing effects of amphiphilic molecules. However to our knowledge, the prior art has not addressed the delivery of particulate material across mucosal membranes. There are many applications where delivery of such particles to or across membranes would be useful. For example the delivery of diagnostic colloids, colloidal therapeutic agents and macromolecular therapeutic agents to target tissues. There is thus a need to effect such delivery and the present invention seeks to address this need

According to a first aspect of the present invention there is provided a delivery formulation for administration to a mucous membrane and which is either, mucoadhesive *per se* or becomes mucoadhesive on contact with a mucous membrane, said formulation comprising a particulate material to be delivered to or across the membrane in a matrix or dose form containing an amphiphilic substance.

According to a second aspect of the present invention there is provided a method of delivering a particulate material to or across a membrane, the method comprising providing a formulation comprised of the particulate material to be delivered in a matrix or dose form containing an amphiphilic substance in contact with the membrane for a period of time for the particulate material to pass in or across the membrane.

The present invention has been based on our finding that mucoadhesive formulations (or formulations which become mucoadhesive in contact with a mucous membrane) containing an amphiphilic substance provide for effective delivery of particulate materials to or across the membrane. Although, as discussed above, amphiphilic substances are known to provide an increase in the permeability of skin and mucosal membranes sufficient to deliver molecules across the membrane, it is surprising that such substances may be used to provide delivery of particulate materials to a membrane. In particular we have found that delivery formulations according to the first aspect of the invention are able to provide prolonged delivery of

the particulate material. Although we do not wish to be bound by any hypothesis, we believe the formulation adheres to the membrane and acts as a reservoir from which the particulate material may be released to or across the membrane. The combination of the amphiphilic substance with the particulate material appears to act to improve the adhesion and in particular to promote the transfer of the particulate material across the membrane. Furthermore the formulation also allows the release of the particulate material (and any active agent associated therewith) over a substantial period of time.

The formulation may be used for delivering a particulate material across a vaginal, intestinal, buccal, nasal or rectal membrane.

Particulate material which may be used in formulations according to the invention will generally have the size of 10nm to 100μm. More preferably, the particulate material will have a size in the range of 100nm to 10μm. The particulate material may for example comprise radioactive particles to be delivered across the mucosal membrane for the purpose of diagnosis or therapy. Thus, for example, the particulate material may be a technetium colloid, irridium or tin. Alternatively the particulate material may be one which is associated, and acts a carrier for, a therapeutic agent to be delivered across the membrane. Thus, for example, the therapeutic agent may be absorbed on the surface of a particulate carrier or contained within the carrier. The carrier may be polymeric or non-polymeric; biodegradable or non-biodegradable; polar, non-polar or non-ionic. Therapeutic agents which may be delivered in this way include proteins, peptides, nucleic acids, biologically engineered molecules and other therapeutic agents prescribed in particulate form.

It is an important feature of the present invention that high molecular weight therapeutic agents may be associated with a particulate carrier and delivered across a mucosal membrane. By high molecular weight we mean at least 5000 daltons although the invention may be used for the delivery of therapeutic agents having a molecular weight in excess of 10000 daltons. Examples of high molecular weight therapeutic agents that may be delivered include proteins and nucleic acids. An advantage of delivering high molecular weight therapeutic agents in association with

the carrier is that the agents may be protected by the carrier from degradation as they pass through the mucosal membrane.

The delivery of diagnostic or therapeutic agents using the techniques of the invention may be for the purpose of topical, local, site-specific or systemic delivery to a subject to be treated.

Formulations in accordance with the invention will preferably comprise 0.01% to 5% by weight of the particulate material to be delivered across the membrane but we do not preclude amounts outside this range.

The formulation of the invention may be one which is mucoadhesive *per se* or one which becomes mucoadhesive on contact with a mucosal membrane. It is particularly preferred that the formulation to be administered is mucoadhesive *per se*. most preferably the formulation of the invention is (for ease of administration) a solid or semi-solid and consists essentially of the particulate material to be delivered, the amphiphilic substance and (optionally) an agent (e.g. water) which generate mucoadhesive properties with the amphiphilic substance and/or particulate material. We do not however preclude the possibility that the formulation of the invention includes conventional excipients such that the formulation is a gel, ointment, suppository, pessary etc.

A wide variety of amphiphilic substances may be used for producing formulations in accordance with the invention. It is however particularly preferred that the amphiphilic substance is a mono- or higher ester of a C_2-C_4 polyhydric alcohol with a carboxylic acid having a chain of 12-22 carbon atoms, said chain possibly containing at least one (preferably cis) olefinic unsaturated bond. Depending on the number of carbon atoms in the polyhydric alcohol, the ester may be a mono-, di-, tri- or tetra-ester. Examples of carboxylic acids with which the polyhydric may be esterified include oleic acid, linoleic acid and other unsaturated fatty acids.

It is particularly preferred in accordance with the invention that the amphiphilic substance is a mono-, di-, or tri-glyceride but not exclusively.

The matrix or dose form incorporating the particulate material may take a number of forms. Thus, for example, certain of the amphiphilic substances contemplated for use in accordance with the invention are capable of forming liquid crystal phases when admixed with water or other polar liquid (for a discussion of the liquid crystal phases which may be formed with amphiphilic substances see for example WO-A-8402076 and WO-A-9534287).

Liquid crystal phases may be formed by both saturated and unsaturated glycerides. Thus saturated monoglycerides of between 12 and 20 carbon atoms form various liquid crystal phases. 12 carbon glycerides (e.g. monolaurin) have only lamellar phase; as the chain length increases to 14 carbon atoms (monomyristin) cubic phases are also formed and further increases to 20 carbon atoms causes reverse hexagonal phases to form in addition to the cubic and lamellar phases.

With unsaturated monoglycerides (at least one double bond) the phases are similar to the saturated monoglycerides, although the unsaturated hydrocarbon chain affects the relative position of the phase boundaries. For example, the trans-unsaturated compound, monelaidin (C18) forms a lamellar phase at temperatures approximately 30 ^{o}C lower than the equivalent saturated monoglyceride monostearin.

Preferred formulations in accordance with the invention comprise a matrix or does form of the amphiphilic substance in a liquid crystal phase, the matrix or dose form incorporating the particulate material to be delivered. The use of such liquid crystal phases for formulations of the invention has been found to be particularly advantageous since they have mucoadhesive properties which make the formulation particularly easy to apply and retain in position. Furthermore such formulations may be semi-solid or solid and easy to handle.

Depending on the relative properties of the amphiphilic substances and the active material added and/or excipients in the formulation, the matrix or dose form may be a lamellar phase, a cubic phase, a reversed hexagonal phase, or a reversed micellar phase. Amphiphilic substances capable of forming liquid crystal phases are generally mono- or higher esters of glycerol with a carboxylic acid having a C_{12-22} carbon chain possibly containing at least one olefinically unsaturated bond.

Formulation in accordance with the invention in which the amphiphilic substance is present as a liquid crystalline phase may be produced by simply mixing the amphiphilic substance, water and particulate material.

Particularly preferred formulations in accordance with the invention comprise, 60 to 80% by weight of glycerol monooleate present as a liquid crystal phase and correspondingly 20% to 40% by weight of water (these percentage being based on the total weight of the glycerol monoleate and water). The use of glycerol monooleate is particularly advantageous in that it is regarded as non-toxic, and biocompatible, and is subject to lipolysis by enzymes present in the various tissues of the body.

Not all amphiphilic substances suitable for use in the invention are capable of forming liquid crystalline phases but nevertheless may be used. Thus, for example triglycerides for which the esterfying, carboxylic acid has a C_{12}-C_{22} carbon chain do not generally form liquid crystalline phases. Formulations in accordance with the invention comprising a triglyceride as matrix may be produced by melting the triglyceride, mixing the melt with the particulate material and allowing the mixture to solidify.

Formulations in accordance with the invention may be used for delivering particulate, material across any mucosal membrane in the human or animal body.

The invention will be further described by way of example only with reference to the following example and accompanying drawings in which Figure 1 illustrates gamma scintigraphs of the radioactivity in a rabbit after the vaginal administration of technetium ^{99m} labelled tin-colloid in a 70/30 wt ratio Myverol 18-99/water gel.

Example 1

A technetium ^{99m} labelled tin-colloid having a particle size of 400nm was incorporated in a composition comprising 70% monolein (myeroids –99) and 30% water.

The resulting formulation was administered intra-vaginally to a rabbit and the delivery of particulate material across the membrane assessed.

1.1 Methods

(i) Monolein/water gels were prepared by melting a known weight of monolein and adding a volume of technetium ^{99m} labelled tin-colloid containing the required amount of activity. A volume of water was then added to produce a 70/30 wt ratio cubic phase gel. The gel was loaded into vaginal applicators until each applicator contained 3.7 MBq of radioactivity.

(ii) A 0.1 ml suspension of technetium ^{99m} labelled tin-colloid, containing 3.7 MBq of radioactivity was administered vaginally to each rabbit using a 1 ml syringe.

1.2 Results and Discussion

The 'visualisation' of a vaginally administered monolein/water gel containing technetium ^{99m} labelled tin-colloid was achieved by gamma scintigraphy. Figure 1 shows that the gel was retained within the vaginal cavity of all rabbits tested over a period of 24 hours.

The movement, or the degree of spreading of the technetium ^{99m} labelled tin-colloid, in the 70/30 wt ratio monolein/water gel was estimated by counting the number of elements within each region of interest on the gamma camera images, which represented the area containing the radioactive formulation.

Technetium ^{99m} labelled tin-colloid was chosen as an insoluble, non-absorbable marker with an average colloid particle size of 400nm. The gamma scintigraphs in Figure 1 were taken after the vaginal administration of technetium ^{99m} labelled tin-colloid to a rabbit in the form of a monolein/water gel (0, 6 and 24 hours

after administration). The gamma scintigraph shows a vaginal site and a second site of activity appearing with time in the liver/spleen area of the rabbit. The appearance of this unexpected second site of activity may be accounted for by the absorption of the technetium ^{99m} labelled tin-colloid through the vaginal membrane and illustrating the effectiveness of the invention in providing for delivery of particles across the membrane.

Further tests indicate that formulations according to the first aspect of the invention are able to provide delivery of particulate material (and active agents associated therewith) over a longer period of time than known formulations (e.g. Witespol W35 pessaries). Therefore an advantage of the formulations according to the invention is that they provide sustained release of the particulate material (and its payload) over a mucous membrane.

CLAIMS

1. A delivery formulation for administration to a mucous membrane and which is either mucoadhesive *per se* or becomes mucoadhesive on contact with a mucous membrane, said formulation comprising a particulate material to be delivered to or across the membrane in a matrix or dose form containing an amphiphilic substance.

2. A formulation as claimed in claim 1 wherein the particulate material has a size of 10nm to 100μm.

3. A formulation as claimed in claim 2 wherein the particulate material has a size of 100nm to 10μm.

4. A formulation as claimed in any one of claims 1 to 3 wherein the amphiphilic substance is a mono- or higher ester of a C_2-C_4 polyhydric alcohol with a carboxylic acid having a chain of 12-22 carbon atoms.

5. A formulation as claimed in claim 4 wherein the carbon chain of the acid has at least one olefinic unsaturated bond.

6. A formulation as claimed in claim 4 or 5 wherein the amphiphilic substance is a mono-, di- or tri-glyceride.

7. A formulation as claimed in any one of claims 1 to 6 which is a solid or semi-solid.

8. A formulation as claimed in any one of claims 1 to 7 which is mucoadhesive in the form in which it is to be administered.

9. A formulation as claimed in claim 8 wherein the amphiphilic substance is present in the matrix or dose form in a liquid crystal phase.

10. A formulation as claimed in claim 9 wherein the matrix or dose form comprises 60 to 80% by weight of glycerol monooleate and 20% to 40% by weight water.

11. A formulation as claimed in claim 9 or 10 wherein the matrix or dose form is a lamellar phase, a cubic phase, a reversed hexagonal phase, or a micellular/reversed micellar phase.

12. A formulation as claimed in any one of claims 1 to 11 which comprises 0.01% to 5% by weight of the particulate material.

13. A formulation as claimed in any one of claims 1 to 12 wherein the particulate material is a radioactive material.

14. A formulation as claimed in any one of claims 1 to 12 wherein the particulate material is a therapeutic agent.

15. A formulation as claimed in any one of claims 1 to 12 wherein the particulate material comprises a particulate carrier and a therapeutic agent associated therewith.

16. A formulation as claimed in claim 15 wherein the therapeutic agent has a molecular weight of at least 50000 daltons.

17. A formulation as claimed in claim 16 wherein the therapeutic agent has a molecular weight of at least 10000 daltons.

18. A formulation as claimed in any one of claims 15 to 17 wherein the therapeutic agent is a nucleic acid or a protein.

19. A method of delivering a particulate material to or across a membrane, the method comprising providing a formulation comprised of the particulate material to

be delivered in a matrix or dose form containing an amphiphilic substance in contact with the membrane for a period of time for the particulate material to pass in or across the membrane.

20. A method according to claim 19 when the membrane is a mucous membrane.

21. A method as claimed in claims 19 or 20 wherein the formulation is as claimed in any one of claims 1 to 18.

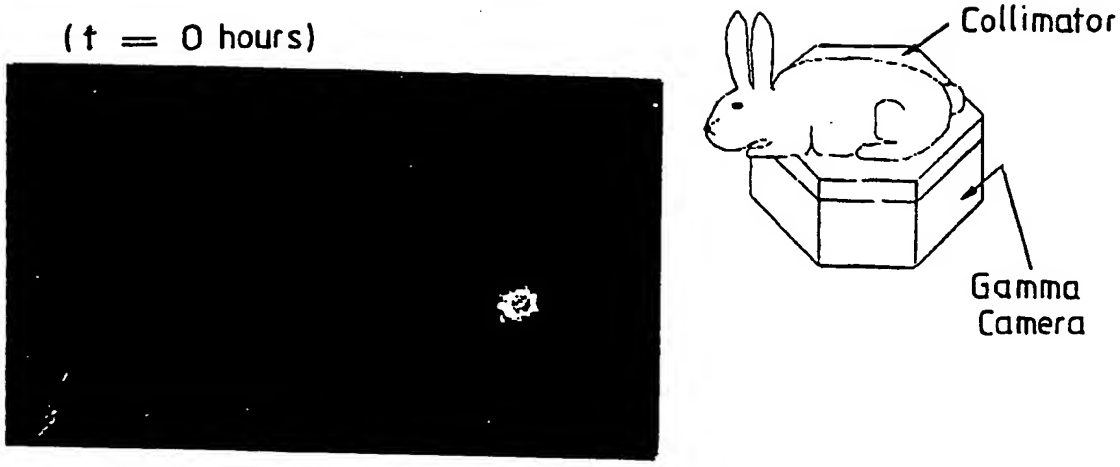

FIG. 1

INTERNATIONAL SEARCH REPORT

In itional Application No
PCT/GB 99/04096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K51/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GERAGHTY PB, ET AL.: "An investigation of the parameters influencing the bioadhesive properties of Myverol 18-99/water gels" BIOMATERIALS, vol. 18, no. 1, 1997, pages 63-67, XP004070846 ISSN 0142-9612 page 65, left-hand column, line 14 - line 32 page 67, left-hand column, line 16 - line 49 --- -/--	1-14, 19-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2000	07/04/2000

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB 99/04096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 34287 A (GS DEV AB ;LJUSBERG WAHREN HELENA (SE); LARSSON KARE (SE)) 21 December 1995 (1995-12-21) cited in the application page 3, line 11 -page 5, line 2 examples 1,3,4,6 claims 1-4,10,13,15,17,20-24 ---	1,4-9, 11,14, 19-21
X	WO 92 09272 A (DUMEX LTD AS) 11 June 1992 (1992-06-11) page 4, line 26 -page 5, line 8 figures 9,10; examples 1,3,4 claims 1,3,6,13-16,18,21-23 ---	1-7,12, 14,19-21
X	WO 97 13528 A (DUMEX LTD AS ;NIELSEN LISE SYLVEST (DK); HANSEN JENS (DK)) 17 April 1997 (1997-04-17) example 13 page 27, line 27 -page 30, line 22 ---	1,4-11, 14,19-21
X	DATABASE WPI Section Ch, Week 199720 Derwent Publications Ltd., London, GB; Class A96, AN 1997-221705 XP002134273 abstract	1,4,6,8, 9,14,15
X	-& PATENT ABSTRACTS OF JAPAN vol. 1997, no. 7, 31 July 1997 (1997-07-31) & JP 09 067273 A (SAGA UNIV), 11 March 1997 (1997-03-11) abstract ---	1,2,8,9, 12,14,15
A	EP 0 122 799 A (AMERSHAM INT PLC) 24 October 1984 (1984-10-24) page 2, line 19 - line 28 examples; tables 1,3 claims 1,6,7,10 -----	1-3,13

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04096

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-21 are directed to a diagnostic method practised on the human/animal body and/or to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

..ternational application No.
PCT/GB 99/04096

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A delivery formulation for administration to a mucous membrane and which is either mucoadhesive per se or becomes mucoadhesive on contact with a mucous membrane, said formulation comprising a particulate material to be delivered to or across the membrane in a matrix or dose form containing an amphiphilic substance.

Prefered formulations in accordance with the invention comprise a matrix or dose form of the amphiphilic substance in a liquid crystal phase, the matrix or dose form incorporating the particulate material to be delivered.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. ational Application No
PCT/GB 99/04096

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